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COMMENTARY

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Fondaparinux in heparin-induced thrombocytopenia: A decade's worth of clinical experience

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Fondaparinux is an antithrombin-dependent, synthetic anti-factor Xa-inhibitor that is used off-label as an alternative anticoagulant in the treatment of life-threatening immune heparin-induced thrombocytopenia (HIT). In their systematic review, Dr. Linkins and colleagues have summarized what is currently known on fondaparinux' safety and efficacy when used in patients with diagnosed and suspected heparin-induced thrombocytopenia.[1] The authors have performed an extensive systematic literature search on data that have been published between 2006 and 2017.

The presented data are important because the current approved alternative anticoagulants for treating this condition have clear limitations: (i) the factor Xa-inhibitor danaparoid is not available in the United States and has been subject to world-wide shortages repeatedly[2]; (ii) use of the thrombin inhibitor argatroban is limited in patients with hepatic insufficiency and aPTT- and INR-confounding may occur in various clinical settings, eg, disseminated intravascular coagulation, during heparin therapy, transition to vitamin K antagonist treatment[3]; (iii) outpatient use of argatroban and bivalirudin is precluded because these drugs require continuous IV infusion and frequent laboratory monitoring; (iv) argatroban, bivalirudin, and danaparoid use is expensive, at least in some jurisdictions[4]; and (v) last but not least, the recombinant hirudin lepirudin is not available on the market anymore since 2012.[2]

However, the main shortcoming of fondaparinux use in HIT is still that there has not been any randomized-controlled trial to date and authorities' approval has not been granted formally.

In order to increase the validity of their study, Dr. Linkins and colleagues have applied strict inclusion and exclusion criteria (ie, fondaparinux as primary anticoagulant with no other alternative anticoagulant allowed for >24 hours; sufficient case number (≥5 patients); laboratory confirmation of HIT (serotonin-release assay, heparin-induced platelet activation assay, or enzyme-linked immunosorbent assay), in combination with clinical symptoms consistent with at least an intermediate pretest probability for HIT (eg, 4Ts score[5]). These rigid patient selection criteria are pivotal when drawing conclusions on general applicability when there are no high quality data from RCTs.

The question is if this has prevented or will prevent physicians in daily practice from applying the drug in patients with suspected or diagnosed heparin-induced thrombocytopenia?

The answer is no, because the users have already "voted with their feet" in favor of fondaparinux[6] with off-label use rates of up to 50% even in patients with high clinical pretest probability of HIT.[7,8] This—besides reports on successful fondaparinux use in HIT—may have been triggered by low therapy cost as compared to approved alternative anticoagulants, being the main cost-drivers in therapy,[4] the ease of subcutaneous administration of the drug, and the lack of need for routine laboratory monitoring and dose adjustment.[1]

Different mechanisms of action, eg, direct oral factor Xa or thrombin inhibition, could overcome the rare, but potential limitation of fondaparinux to cause HIT itself,[9] and direct oral anticoagulants have been widely available. However, the authors of this review have already reported the same difficulties of identifying and recruiting HIT patients for a robust prospective trial using direct oral anticoagulants that already apply for fondaparinux.[10] Together with the manufacturer's lack of interest in investing into research to expand indications this will pose the same problem as already observed with fondaparinux: there might be no RCTs of high quality available in the future and gathering clinical experience with direct oral anticoagulants to the same extent as for fondaparinux is expanding only slowly. Thus, the data presented by the authors of a comparable efficacy in preventing thromboembolic complications and safety with respect to bleeding complications, represent the largest body of evidence to date for an off-label alternative anticoagulant in the treatment of HIT.

The authors' compilation of clinical data on HIT management with fondaparinux might help to harmonize current treatment recommendations. Looking at the different guideline recommendations from various professional or governmental associations reveals that these differ not only in methodological aspects but as well in their conclusions drawn.[11] While some guidelines recommend the use of fondaparinux,[12–14] fondaparinux carries a level 2C recommendation from the American College of Chest Physicians (ACCP).[15] However, ACCP held out the prospect of readjusting their recommendations once more clinical evidence has emerged. The data of Linkins and colleagues might now contribute to start this discussion and to put current fondaparinux off-label practice on a safer medico-legal level for the treating physicians. Advocacy in favor of fondaparinux already when underlying HIT is suspected and thereby "legalizing" its use might face the clinical problem that HIT diagnosis and therapy is often delayed.[16] However, one must take into account that "true" HIT is still rare compared to the number of patients with HIT suspicion and that HIT is often overdiagnosed and overtreated.[17,18] Thus, fondaparinux use will mostly concern patients with HIT suspicion.

Among numerous patients with suspected or diagnosed HIT who were treated with fondaparinux, dosing was inconsistent.[8,19,20] This will remain a future challenge for research against the background of clinical HIT probability, thromboembolic complications, and bleeding risk.

ADDENDUM

The release of the American Society of Hematology (ASH) 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia (HIT),[21] after this writing, recommended the use of fondaparinux in the treatment of acute HIT with thromboembolic complications. Despite the reference to the very low certainty in the evidence about effects, no preference is suggested for non-heparin anticoagulants over fondaparinux in these guidelines. However, the choice of agent may be influenced by drug factors (availability, cost, ability to monitor the anticoagulant effect, route of administration, and half-life), patient factors (kidney function, liver function, bleeding risk, clinical stability, and need for urgent procedures), and experience of the clinician.

RELATIONSHIP DISCLOSURE

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REFERENCES

1. Linkins L-A, Hu G, Warkentin TE. Systematic review of fondaparinux for heparin-induced thrombocytopenia: when there are no randomized controlled trials. Res Pract Thromb Haemost. 2018;2(4):678–83.
2. Alatri A, Armstrong AE, Greinacher A, et al. Results of a consensus meeting on the use of argatroban in patients with heparin-induced thrombocytopenia requiring antithrombotic therapy – a European Perspective. Thromb Res. 2012;129:426–33.
3. Warkentin TE. Anticoagulant failure in coagulopathic patients: PTT confounding and other pitfalls. Expert Opin Drug Saf. 2014;13:25–43.
4. Aljabri A, Huckleberry Y, Karnes JH, et al. Cost-effectiveness of anticoagulants for suspected heparin-induced thrombocytopenia in the United States. Blood. 2016;128:3043–51.
5. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost. 2006;4:759–65.
6. Warkentin TE. Voting with your fondaparinux. Thromb Res. 2014;134:3–4.
7. Schindewolf M, Steindl J, Beyer-Westendorf J, et al. Frequent off-label use of fondaparinux in patients with suspected acute heparin-induced thrombocytopenia (HIT) – findings from the GerHIT multi-centre registry study. Thromb Res. 2014;134:29–35.
8. Schindewolf M, Steindl J, Beyer-Westendorf J, et al. Use of fondaparinux off-label or approved anticoagulants for management of heparin-induced thrombocytopenia. J Am Coll Cardiol. 2017;70:2636–48.
9. Warkentin TE. Fondaparinux: does it cause HIT? Can it treat HIT? Expert Rev Hematol. 2010;3:567–81.
10. Linkins LA, Warkentin TE, Pai M, et al. Rivaroxaban for treatment of suspected or confirmed heparin-induced thrombocytopenia study. J Thromb Haemost. 2016;14:1206–10.
11. Wang Y, Ye ZK, Li JF, Cui XL, Liu LH. Heparin-induced thrombocytopenia: a critical appraisal of clinical practice guidelines with the AGREE II instrument. Thromb Res. 2018;166:10–8.
12. Watson H, Davidson S, Keeling D. Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition. Br J Haematol. 2012;159:528–40.
13. Cuker A, Crowther MA. American Society of Hematology. 2013 Clinical Practice Guideline on the Evaluation and Management of Adults with Suspected Heparin-Induced Thrombocytopenia (HIT). Available from http://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx [Accessed 2018 October 12].
14. Thrombosis Canada. Heparin-induced thrombocytopenia (HIT). Available from https://thrombosiscanada.ca/clinicalguides/# [Accessed 2018 October 12].
15. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e495S–530S.
16. Crespo EM, Oliveira GB, Honeycutt EF, et al. Evaluation and management of thrombocytopenia and suspected heparin-induced thrombocytopenia in hospitalized patients: the Complications After Thrombocytopenia Caused by Heparin (CATCH) registry. Am Heart J. 2009;157:651–7.
17. Harada MY, Hoang DM, Zaw AA, et al. Overtreatment of heparin-induced thrombocytopenia in the surgical ICU. Crit Care Med. 2017;45:28–34.
18. Lo GK, Sigouin CS, Warkentin TE. What is the potential for overdiagnosis of heparin-induced thrombocytopenia? Am J Hematol. 2007;82:1037–43.
19. Kang M, Alahmadi M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux for the treatment of suspected heparin-induced

thrombocytopenia: a propensity score–matched study. Blood. 2015;125:924–9.
20. Linkins LA, Bates SM, Lee AY, Heddle NM, Wang G, Warkentin TE. Combination of 4Ts score and PF4/H-PaGIA for diagnosis and management of heparin-induced thrombocytopenia: prospective cohort study. Blood. 2015;126:597–603.
21. Cuker A, Arepally GM, Chong BH, Cines DB, Greinacher A, Gruel Y, Linkins LA, Rodner SB, Selleng S, Warkentin TE, Wex A, Mustafa RA, Morgan RL, Santesso N. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2:3360–92.